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Treatment and Mortality in Men with Localized Prostate Cancer: A Population-Based Study in California

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Abstract

Purpose—To provide patients and physicians with population-based estimates of mortality from prostate cancer or other causes depending upon the primary treatment modality, stratified by patient age, tumor stage and grade.

Methods—We conducted a 10-year competing-risk analysis of 45,440 men diagnosed with clinically localized (T1 or T2) prostate cancer in California during 1995–1998. Information on patient characteristics, primary treatment and cause of death was obtained from the California Cancer Registry.

Results—In this population-based cohort, the most common primary treatment was surgery (40.4%), followed by radiotherapy (29.1%), conservative management (20.8%), and androgen deprivation therapy (ADT) monotherapy (9.8%). Prostate cancer mortality differed significantly ($p < 0.0001$) across treatment groups among patients <80 years at diagnosis with moderately or poorly differentiated disease; the 10-year disease-specific mortality rates were generally highest for men treated with ADT monotherapy [range: 3.3% (95% CI=0.8–12.5%) to 53.8% (95% CI=34.4–72.2%)], intermediate for men treated with conservative management [range: 1.7% (95% CI=0.7–4.6%) to 30.0% (95% CI=16.2–48.8%] or radiotherapy [range: 3.2% (95% CI=1.8–5.5%) to 18.3% (95% CI=15.1–22.0%)], and lowest for men treated with surgery [range: 1.2% (95% CI=0.8–1.7%) to 11.0% (95% CI=8.4–14.2%)].

Conclusion—The cause-specific mortality estimates provided by this observational study can help patients and physicians better understand the expected long-term outcomes of localized prostate cancer given the initial treatment choice and practice patterns in the general population.

Keywords

Prostate cancer; treatment; mortality; cohort study; California Cancer Registry

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INTRODUCTION

Over the past two decades, widespread application of prostate specific antigen (PSA) testing has shifted the clinical landscape of prostate cancer to earlier stages of the disease.[1] In 2012, over 241,000 U.S. men were diagnosed with prostate cancer, approximately 80% of whom had localized (stage T1 or T2) disease.[2] To date, randomized trials have shown little survival benefit with PSA testing, indicating that many indolent tumors are being overdetected and overtreated.[3,4] The optimal treatment of localized prostate cancer remains controversial.[5] Standard treatment options include surgery, radiation, and conservative management (active surveillance or watchful waiting).[6] Additionally, primary treatment with androgen deprivation therapy (ADT) is frequent despite lack of evidence from clinical trials to support its use as monotherapy for localized prostate cancer.[7]

Randomized controlled trials are currently underway that will ultimately help determine whether or not treatment reduces mortality in men with localized prostate cancer. Observational studies have suggested that active surveillance of low-risk patients may be a safe alternative to initial treatment and may preserve quality of life.[8] However, recent results from randomized trials of radical prostatectomy compared with observation demonstrated that surgery significantly reduced prostate cancer mortality among men younger than 65 years at diagnosis[9] or high-risk disease,[10] indicating that some patient subgroups may have a survival benefit from aggressive treatment.

The natural history of prostate cancer is heterogeneous, and most men with localized prostate cancer will die of causes other than their disease.[11] Therefore, knowledge of a man's absolute risks of dying from prostate cancer versus other causes is critical for making informed treatment choices. We assembled a population-based cohort of 45,440 men representing virtually all men diagnosed with clinically localized prostate cancer in California during 1995–1998. Our aim was to describe the absolute 10-year mortality from prostate cancer or competing causes of death in patient populations initially treated with surgery, radiation, ADT monotherapy or conservative management.

PATIENTS AND METHODS

Study population

We identified all men diagnosed with a first primary invasive adenocarcinoma of the prostate (International Classification of Diseases for Oncology, 3rd edition [ICD-O-3] site code 61.9; morphology code 8140) in California between January 1, 1995 and December 31,1998 using data from the California Cancer Registry (CCR; http://www.ccrcal.org/), which captures 99% of cancer diagnoses state-wide. We chose the years 1995–1998 in order to obtain at least 10 years of follow-up, needed because of low disease-specific mortality among men with localized prostate cancer, and to represent the period following the introduction of PSA testing, when stage migration had largely stabilized.[12] Eligible patients were diagnosed with clinical stage T1 or T2 disease (N=55,082). Exclusion criteria included: ambiguous stage ("localized, not otherwise specified"; N=5111); diagnosis on autopsy or death certificate only (N=46); "unknown" or "other" race (N=1799); unknown tumor grade (N=1097); lost to follow-up within 10 years (N=1119); invalid follow-up dates (N=1); and cause of death unavailable or unknown (N=358). We also excluded cases who received chemotherapy (N=111) within 4 months of diagnosis because chemotherapy is not standard treatment for localized prostate cancer and could reflect more advanced disease. The final study population consisted of 45,440 men. This study was approved by the Institutional Review Board of the Cancer Prevention Institute of California.

Outcome ascertainment

The CCR regularly updates vital status information through hospital follow-up and linkages with state and national databases and agencies. Follow-up information was available through May 31, 2010; the median follow-up period was 138 months after diagnosis. Cases were classified as alive or deceased within 10 years of diagnosis. The cause of death was classified as prostate cancer or other competing causes based upon the underlying cause of death on the death certificate, which has been shown to be a reliable means of ascertaining death due to prostate cancer.[13,14]

Patient characteristics

Patient diagnoses and demographic data are routinely collected by the CCR in accordance with guidelines of the National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER; http://seer.cancer.gov/) program and the California Department of Public Health. For this study, age at diagnosis was categorized in 10-year groups (<50, 50–59, 60–69, 70–79, 80+). Tumor stage was categorized as American Joint Committee on Cancer (AJCC) stage T1 (clinically inapparent) or T2 (clinically apparent, confined to prostate) using the SEER clinical extent-of-disease information. Tumor grade was categorized as well-differentiated (Gleason score 2–4), moderately differentiated (Gleason score 5–7), or poorly differentiated (Gleason score 8–10) as defined by SEER.[15] Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Hispanic, or Asian/Pacific Islander.[16] Socioeconomic status (SES) was measured using a neighborhood-level index that incorporates Census data on education, income, occupation, and housing costs at the census block-group level.[17] Each case was assigned to his neighborhood SES quintile based on the distribution of the composite SES index across California.

The CCR collects information on the first course of treatment for prostate cancer that was administered or initiated within four months of diagnosis. Primary treatment was categorized as surgery, radiotherapy, ADT monotherapy, or conservative management (no therapy within four months of diagnosis). Surgery denotes procedures such as prostatectomy that ablate the organ; patients classified as having received surgery included those who also received adjuvant radiation and/or ADT. Radiotherapy denotes external beam radiation and/or brachytherapy; patients classified as having received radiotherapy included those who received both radiotherapy and ADT. ADT monotherapy denotes initial treatment with only hormone therapy or endocrine surgery (orchiectomy).

Statistical Analysis

Competing risks of death from prostate cancer or other causes were estimated for each of the four primary treatment groups, stratified by age, grade, and stage at diagnosis. Cumulative incidence functions were used to estimate the absolute risk of dying of either prostate cancer or other causes, and global tests of the equality of estimated mortality curves across treatment groups were performed using the cmprsk package[18,19] implemented in R (R Foundation for Statistical Computing, Vienna, Austria). 95% confidence intervals (CI) for 10-year cumulative mortality estimates were constructed using the delta method and log-odds transformation to obtain estimates between 0 and 1.[20] We assessed the sensitivity of results to potential misclassification of clinical stage by comparing results in the surgery group overall to the subset of 9,665 surgically treated men with pathologically confirmed localized disease. All p-values were 2-sided.

RESULTS

As of May 31, 2010, 15,143 deaths had occurred among the 45,440 men diagnosed with clinically localized prostate cancer in California during 1995–1998, and 2,720 (18%) of

these deaths were attributed to prostate cancer (Table 1). About half of all cases had stage T2 disease at diagnosis and 11.7% of all tumors were well differentiated. The most common primary treatment was surgery (40.4%), followed by radiation (29.1%), conservative management (20.8%), and ADT monotherapy (9.8%). Among surgically treated patients, 644 (3.5%) received adjuvant radiotherapy only, 2,157 (11.8%) received adjuvant ADT only, and 250 (1.4%) received both radiotherapy and ADT within four months of diagnosis. A substantially greater proportion of men who underwent primary radiotherapy received adjuvant ADT (40.7%) compared with men who underwent surgery (13.1%).

Characteristics of patients in the four primary treatment groups are shown in Table 1. Patients who initially received conservative management tended to be older (median age 73 years) at diagnosis, and to have well-differentiated and T1 disease. Surgically treated patients were youngest (median age 64 years) at diagnosis, and least likely to have well-differentiated tumors at diagnosis. Patients treated with radiation were intermediate to the other treatment groups with respect to age (median 70 years) at diagnosis and tumor grade, but were the most likely to have T2 disease at diagnosis. Patients who received ADT monotherapy were the oldest (median age 75 years) at diagnosis, and most likely to have poorly differentiated tumors.

Table 2 shows the sample size and proportion of the 45,440 men with clinically localized prostate cancer that died from their disease or other causes, stratified by age at diagnosis, tumor grade and stage. In general, men with localized prostate cancer were far more likely to die from other causes than from their disease, except for men <60 years diagnosed with poorly differentiated disease. As expected, the proportion of men who died from prostate cancer generally increased with older age, higher grade, and clinically apparent disease at diagnosis. The 10-year cumulative mortality rate among all men with localized prostate cancer was 6.5% (95% CI, 6.2–6.7%) for prostate cancer and 27.0% (95% CI, 26.5–27.4%) for competing causes of death. Patients with well, moderately, or poorly differentiated disease respectively had 10-year cumulative mortality rates of 2.7% (95% CI, 2.3–3.2%), 4.3% (95% CI, 4.1–4.5%), and 15.1% (95% CI, 14.3–15.9%) for prostate cancer and 33.5% (95% CI, 32.2–34.8%), 26.5% (95% CI, 26.0–26.9%), and 29.0% (95% CI, 28.0–30.0%) for competing causes of death.

Figure 1 shows the estimated mortality curves for prostate cancer or competing causes of death among patients in each of the four primary treatment groups, stratified by age, grade, and stage at diagnosis. Prostate cancer mortality curves differed significantly across treatment groups among men <80 years with moderately or poorly differentiated disease (Table 3). However, no significant differences in prostate cancer mortality were found across treatment groups for men <70 years with well-differentiated disease or ≥80 years with moderately or poorly differentiated disease (Table 3). The small number of prostate cancer deaths among men with well-differentiated disease and surgically treated men ≥80 years limited the reliability of mortality estimates in these groups.

Prostate cancer mortality was highest among patients who received ADT monotherapy (Figure 1B) across all strata, and was especially high among men <70 years diagnosed with poorly differentiated disease. Men who received ADT monotherapy or conservative management (Figure 1A) both experienced relatively high mortality from causes other than their disease. Prostate cancer mortality was generally similar in men who received conservative management or radiotherapy (Figure 1C), although men diagnosed at age ≥70 or with poorly differentiated disease who were treated with radiotherapy tended to have lower mortality rates than those who received conservative management. Surgically treated men (Figure 1D) had the lowest mortality from prostate cancer among men <80 years with moderately or poorly differentiated disease. Sensitivity analyses among men with

pathologically confirmed localized disease following radical prostatectomy with lymph node dissection showed that prostate cancer mortality was slightly lower but similar to that for all surgically treated men (data not shown), indicating that misclassification of clinical stage did not have a substantial impact on the results.

DISCUSSION

Determining the optimal treatment of localized prostate cancer is a great challenge for physicians and patients, given limited evidence to date regarding the comparative effectiveness of treatment alternatives. In this population-based cohort of 45,440 California men with clinically localized prostate cancer, we found that patients who were initially treated with surgery, radiotherapy, ADT monotherapy, or conservative management differed significantly with respect to their ten-year risk of dying from prostate cancer or competing causes. To our knowledge, this large observational study is the first to compare mortality estimates among men with clinically localized prostate cancer treated with surgery, radiation, conservative management, as well as ADT monotherapy. This information provides a framework for understanding the expected long-term outcomes of localized prostate cancer given the initial treatment choice and practice patterns in the general population.

Although ADT monotherapy is not recommended for localized prostate cancer,[6] it was received by 9.8% of the men in this cohort. This proportion was slightly higher than the estimate of 7.6% from a SEER Patterns of Care study (POC) in which treatment data from medical records was supplemented by forms sent to physicians for men diagnosed with localized disease in 1998.[21] We found that combined therapy with ADT was utilized by 40.7% and 13.1% of patients treated with radiotherapy and surgery, respectively. A randomized trial of radiotherapy combined with ADT versus radiotherapy alone for localized prostate cancer reported that combined therapy significantly decreased disease-specific mortality.[22] In contrast, several randomized trials of neoadjuvant ADT before surgery have not shown a survival benefit,[23,24,25] which may help explain the substantially greater frequency of ADT use among men treated with radiotherapy versus surgery. We found that men treated with ADT monotherapy had the highest disease-specific mortality across all strata of age, grade, and stage at diagnosis, consistent with previous studies including one randomized trial that did not find a survival benefit with ADT monotherapy.[7,26,27] It is possible that men treated with ADT monotherapy have higher-risk disease, contributing to poorer outcomes. However, in light of evidence that ADT is adversely associated with osteoporosis,[28] cardiovascular disease and diabetes,[29,30] and the lack of evidence of a survival benefit from ADT monotherapy, it is especially important for patients and physicians to be aware of the long-term outcomes among men in this group when considering treatment options.

Approximately 70% of California men with localized prostate cancer underwent attempted curative treatment with surgery (40.4%) or radiation (29.1%). We found that men <80 years with moderately to poorly differentiated disease treated with surgery had the lowest mortality from prostate cancer. Patients ≥70 years initially treated with radiotherapy versus conservative managment generally had lower disease-specific mortality, although the differences were not significant among men ≥80 years. These findings are consistent with evidence from randomized trials that treatment with surgery[9] or high-dose radiotherapy[31,32,33,34,35] improves outcomes of localized prostate cancer. In subgroup analyses from randomized trials, surgery significantly reduced overall and disease-specific mortality only among men <65 years,[9] whereas radiation combined with ADT versus radiation alone significantly reduced disease-specific mortality only among men ≥70 years.[22] Thus, evidence from both clinical trials and observational studies suggests that active

treatment with radiotherapy may be more effective in older men, whereas surgery may be more effective in younger men.[36] Alternative explanations for the better outcomes among actively treated men include patient selection based on life expectancy ≥10 years, absence of comorbidities that contraindicate treatment,[6] or other unmeasured factors associated with improved prostate cancer survival.

We found no significant differences in prostate cancer mortality across treatment groups among men <70 with well-differentiated disease or ≥80 years with moderately or poorly differentiated disease, suggesting that conservative management is a safe and effective choice for these patients. The mortality estimates for California men who underwent initial conservative management was similar to U.S. men diagnosed with localized prostate cancer during 1992–2002 who were managed without surgery or radiation but may have received ADT within six months of diagnosis.[37] Studies of SEER treatment data for prostate cancer have shown that, whereas surgery and radiation are well captured,[38,39] hormonal therapy may be underascertained by medical record abstraction compared to patient self-report.[40] Thus, one potential limitation of the present study is that the conservative management group may include some men who received ADT. However, the similar proportion of men who received initial ADT monotherapy in this study compared to a SEER POC study in 1998 that supplemented registry data with physician surveys[21] suggests that the degree of ADT underascertainment by the CCR may be relatively modest. The high mortality from non-prostate cancer causes among men who initially received conservative management or ADT monotherapy may reflect high comorbidity contraindicating aggressive treatment. Greater comorbidity has been associated with higher overall mortality as well as lower prostate-cancer-specific mortality.[41]

The main limitation of this observational study was that, without randomization, primary treatment groups may differ systematically with respect to unmeasured characteristics such as comorbidities that influence mortality. Thus, the data presented here are intended to describe mortality given a patient's initial treatment choice and practice patterns in the general population, and should not be interpreted as a quantification of treatment effects. Additionally, the CCR, like other SEER registries, does not have information on PSA values at diagnosis, and Gleason 5–7 tumors were collapsed as moderately differentiated disease, potentially obscuring survival differences in this group. The main strengths of this observational cohort study are the large sample size, follow-up for over ten years, and population-based setting, with capture of nearly all prostate cancer cases diagnosed in California. Thus, the findings are robust and broadly applicable, and are not restricted to specific clinics or age groups as is often the case for clinical trials or Medicare claims-based studies.

This study provides population-based estimates of a man's absolute risk of dying from prostate cancer or other causes within ten years of his diagnosis with localized prostate cancer depending upon his initial treatment choice and disease characteristics. These data may help patients and physicians to better understand the expected long-term outcomes of clinically localized prostate cancer in the context of practice patterns in the general population. Additional studies will be needed to characterize mortality trends as practice patterns change over time.

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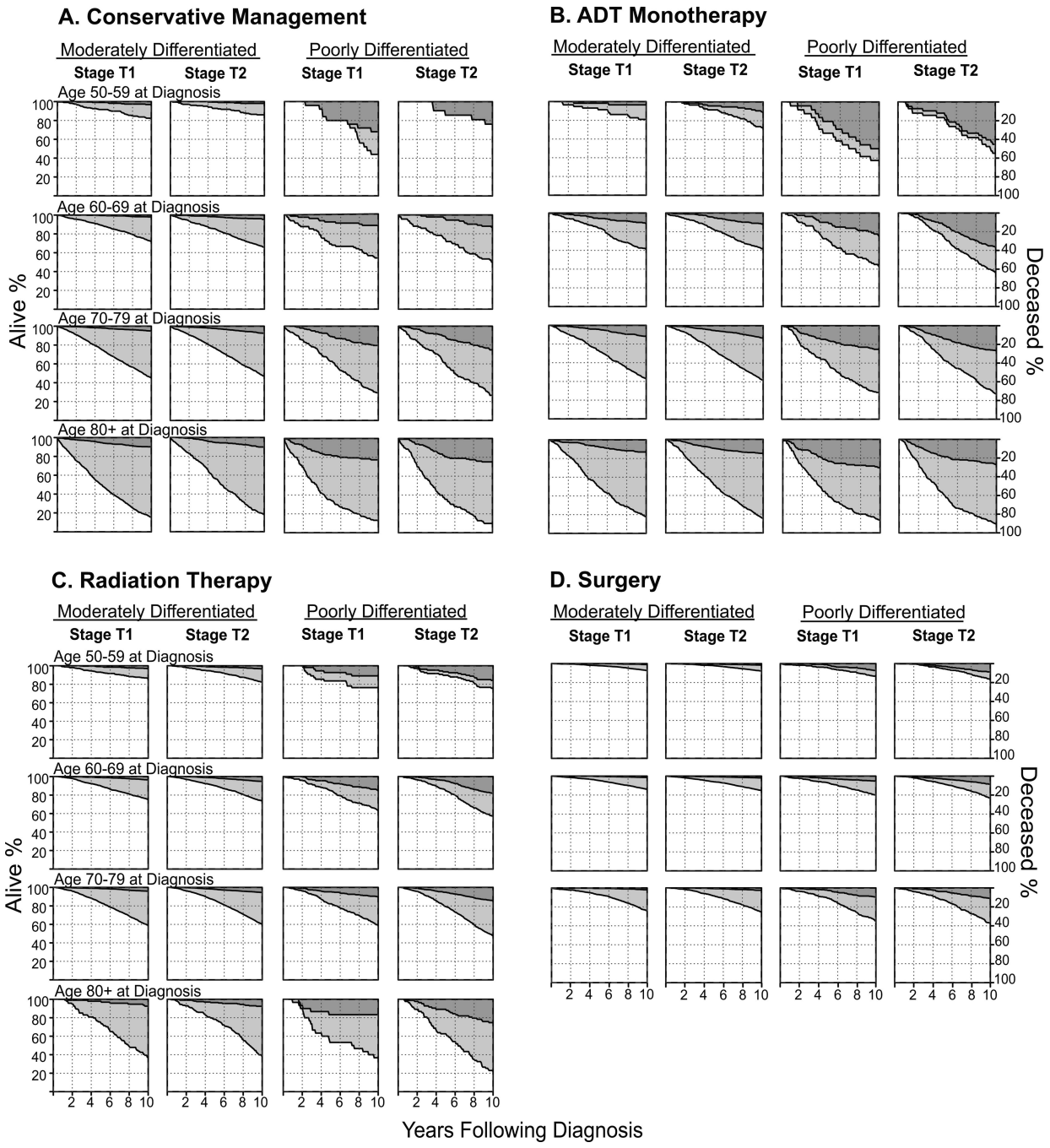

Figure 1.

Competing risk of death among men with localized prostate cancer who received primary treatment with conservative management (A), ADT monotherapy (B), radiation therapy (C) or surgery (D), stratified by age at diagnosis, tumor stage and grade. Prostate cancer mortality (dark grey), non-prostate cancer mortality (light grey), survival probability (white).

Table 1

Characteristics of California men diagnosed with clinically localized prostate cancer in 1995–1998, overall and by primary treatment.

Characteristics	All cases N = 45,440		Conservative management N = 9,435		Surgery N = 18,355		Radiation therapy N = 13,203		ADT monotherapy N = 4,447	
	n	%	n	%	n	%	n	%	n	%
10-year survival										
Alive	30,297	(66.7)	4575	(48.5)	15412	(84.0)	8651	(65.5)	1659	(37.3)
Died of prostate cancer	2,720	(6.0)	611	(6.5)	537	(2.9)	815	(6.2)	757	(17.0)
Died of other causes	12,423	(27.3)	4249	(45.0)	2406	(13.1)	3737	(28.3)	2031	(45.7)
Age at diagnosis (years)										
<50	797	(1.8)	64	(0.7)	614	(3.3)	102	(0.8)	17	(0.4)
50–59	7,005	(15.4)	654	(6.9)	4798	(26.1)	1309	(9.9)	244	(5.5)
60–69	17,735	(39.0)	2457	(26.0)	9554	(52.1)	4784	(36.2)	940	(21.1)
70–79	16,268	(35.8)	4329	(45.9)	3349	(18.2)	6576	(49.8)	2014	(45.3)
80+	3,635	(8.0)	1931	(20.5)	40	(0.2)	432	(3.3)	1232	(27.7)
Race/ethnicity										
Non-Hispanic White	34,218	(75.3)	6838	(72.5)	13881	(75.6)	10156	(76.9)	3343	(75.2)
Non-Hispanic Black	3,931	(8.7)	922	(9.8)	1466	(8.0)	1150	(8.7)	393	(8.8)
Hispanic	4,936	(10.9)	1106	(11.7)	2127	(11.6)	1232	(9.3)	471	(10.6)
Asian/Pacific Islander	2,355	(5.2)	569	(6.0)	881	(4.8)	665	(5.0)	240	(5.4)
Neighborhood SES (quintile)										
1 (lowest)	5,114	(11.3)	1438	(15.2)	1738	(9.5)	1294	(9.8)	644	(14.5)
2	7,700	(16.9)	1846	(19.6)	2869	(15.6)	2161	(16.4)	824	(18.5)
3	9,144	(20.1)	1953	(20.7)	3461	(18.9)	2784	(21.1)	946	(21.3)
4	10,415	(22.9)	1989	(21.1)	4324	(23.6)	3116	(23.6)	986	(22.2)
5 (highest)	13,067	(28.8)	2209	(23.4)	5963	(32.5)	3848	(29.1)	1047	(23.5)
Gleason score, tumor grade										
2–4, well-differentiated	5,330	(11.7)	2515	(26.7)	1016	(5.5)	1423	(10.8)	376	(8.5)
5–7, moderately differentiated	32,092	(70.6)	5961	(63.2)	13800	(75.2)	9540	(72.3)	2791	(62.8)
8–10, poorly differentiated	8,018	(17.6)	959	(10.2)	3539	(19.3)	2240	(17.0)	1280	(28.8)
Clinical stage										
T1	21,965	(48.3)	5917	(62.7)	9309	(50.7)	4993	(37.8)	1746	(39.3)
T2	23,475	(51.7)	3518	(37.3)	9046	(49.3)	8210	(62.2)	2701	(60.7)
Adjuvant ADT use										
No	33,213	(73.1)			15948	(86.9)	7830	(59.3)		
Yes	12,227	(26.9)			2407	(13.1)	5373	(40.7)		

ADT = androgen deprivation therapy; SES = socioeconomic status.

Table 2

Sample sizes by age and vital status as of May 2010 among California men diagnosed with clinically localized prostate cancer in 1995–1998.

Grade and stage	Age at diagnosis, years, n (%)				
	<60 n = 7,802	**60–69 n = 17,735**	**70–79 n = 16,268**	**80+ n = 3,635**	**All ages N = 45,440**
Gleason 2–4, T1 and T2					
Alive	616 (89.5)	1448 (78.1)	1242 (56.4)	112 (19.0)	3418 (64.1)
Died of prostate cancer	9 (1.3)	39 (2.1)	66 (3.0)	30 (5.1)	144 (2.7)
Died of other causes	63 (9.2)	366 (19.8)	893 (40.6)	446 (75.9)	1768 (33.2)
Gleason 5–7, T1					
Alive	2633 (90.8)	5036 (80.7)	2873 (57.1)	206 (17.8)	10748 (70.2)
Died of prostate cancer	47 (1.6)	143 (2.3)	234 (4.7)	121 (10.5)	545 (3.6)
Died of other causes	219 (7.6)	1059 (17.0)	1921 (38.2)	828 (71.7)	4027 (26.3)
Gleason 5–7, T2					
Alive	2708 (89.3)	5192 (78.0)	3511 (58.1)	215 (20.7)	11626 (69.3)
Died of prostate cancer	67 (2.2)	247 (3.7)	376 (6.2)	123 (11.9)	813 (4.8)
Died of other causes	257 (8.5)	1217 (18.3)	2160 (35.7)	699 (67.4)	4333 (25.8)
Gleason 8–10, T1					
Alive	397 (80.0)	862 (72.5)	574 (50.7)	57 (15.5)	1890 (59.4)
Died of prostate cancer	58 (11.7)	103 (8.7)	161 (14.2)	93 (25.3)	415 (13.0)
Died of other causes	41 (8.3)	224 (18.8)	397 (35.1)	217 (59.1)	879 (27.6)
Gleason 8–10, T2					
Alive	538 (78.3)	1178 (65.5)	838 (45.1)	61 (12.5)	2615 (54.1)
Died of prostate cancer	100 (14.6)	261 (14.5)	316 (17.0)	126 (25.8)	803 (16.6)
Died of other causes	49 (7.1)	360 (20.0)	706 (38.0)	301 (61.7)	1416 (29.3)

Table 3

Ten-year disease-specific cumulative mortality (with 95% confidence intervals) among men with localized prostate cancer stratified by primary treatment, age, grade, and stage at diagnosis.

Grade, stage, and treatment	N	<60 years	p*	N	60–69 years	p*	N	70–79 years	p*	N	80+ years	p*
Gleason 2–4, T1–T2			0.52			0.24			0.0001			<0.0001
Conservative management	185	0.5 (0.1–3.8)		679	1.8 (1.0–3.1)		1180	3.1 (2.2–4.2)		471	3.2 (1.9–5.2)	
Surgery	301	1.3 (0.5–3.5)		544	1.5 (0.7–2.9)		165	0.6 (0.1–4.2)		6	NE	
Radiation therapy	175	1.7 (0.6–5.2)		549	2.9 (1.8–4.7)		672	2.1 (1.2–3.5)		27	7.4 (1.8–25.9)	
ADT monotherapy	27	3.7 (0.5–22.7)		81	3.7 (1.2–10.9)		184	8.2 (5.0–13.1)		84	15.5 (9.2–25.0)	
Gleason 5–7, T1			0.008			<0.0001			<0.0001			0.33
Conservative management	248	2.8 (1.3–5.8)		925	1.9 (1.2–3.1)		1586	5.0 (4.1–6.2)		751	9.9 (7.9–12.2)	
Surgery	2211	1.2 (0.8–1.7)		3689	1.4 (1.1–1.8)		1205	2.0 (1.3–3.0)		11	9.1 (1.1–47.9)	
Radiation therapy	380	3.2 (1.8–5.5)		1386	3.5 (2.6–4.6)		1714	4.0 (3.2–5.1)		94	7.4 (3.6–14.9)	
ADT monotherapy	60	3.3 (0.8–12.5)		238	10.9 (7.5–15.6)		523	11.7 (9.2–14.7)		299	13.0 (9.7–17.4)	
Gleason 5–7, T2			<0.0001			<0.0001			<0.0001			0.04
Conservative management	230	1.7 (0.7–4.6)		680	4.9 (3.5–6.7)		1155	7.4 (6.1–9.1)		386	10.4 (7.7–13.8)	
Surgery	2021	1.4 (1.0–2.1)		3494	1.8 (1.4–2.3)		1157	2.5 (1.7–3.6)		12	8.3 (1.1–43.8)	
Radiation therapy	679	3.4 (2.3–5.0)		2126	5.1 (4.2–6.1)		2963	5.4 (4.6–6.3)		198	8.1 (5.0–12.8)	
ADT monotherapy	102	10.8 (6.1–18.5)		356	11.8 (8.8–15.6)		772	13.1 (10.9–15.7)		441	15.0 (11.9–18.6)	
Gleason 8–10, T1			<0.0001			<0.0001			<0.0001			0.29
Conservative management	30	30.0 (16.2–48.8)		81	11.1 (5.9–20.1)		201	20.4 (15.4–26.6)		190	22.6 (17.2–29.2)	
Surgery	383	7.6 (5.3–10.7)		802	5.1 (3.8–6.9)		375	9.6 (7.0–13.0)		7	28.6 (6.2–70.9)	
Radiation therapy	57	10.5 (4.8–21.7)		226	14.6 (10.6–19.8)		378	10.3 (7.6–13.8)		30	16.7 (7.0–34.8)	
ADT monotherapy	26	53.8 (34.4–72.2)		80	25.0 (16.7–35.7)		178	25.3 (19.4–32.2)		140	30.7 (23.6–38.9)	
Gleason 8–10, T2			<0.0001			<0.0001			<0.0001			0.64
Conservative management	25	24.0 (11.0–44.7)		92	13.0 (7.5–21.7)		207	25.1 (19.7–31.5)		133	24.8 (18.2–32.9)	
Surgery	496	10.3 (7.9–13.3)		1025	8.9 (7.3–10.8)		447	11.0 (8.4–14.2)		4	NE	
Radiation therapy	120	18.3 (12.4–26.3)		497	18.3 (15.1–22.0)		849	14.1 (11.9–16.6)		83	25.3 (17.0–35.9)	
ADT monotherapy	46	45.7 (31.8–60.2)		185	36.2 (29.6–43.4)		357	26.6 (22.3–31.4)		268	26.9 (21.9–32.5)	

*Global test of differences among the overall mortality curves for the four treatment groups

NE = not estimable